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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,676	02/28/2002	Iris Ziegler	148/50932	2539

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EXAMINER	
FUBARA, BLESSING M	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,676	ZIEGLER ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Examiner acknowledges receipt of IDS and priority papers filed 02/28/02 and fess and declaration filed 05/22/02.

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. It is noted that a translation of the priority document is not provided.

2. The international search report listed on the information disclosure statement filed 02/28/02 is not prior art. If applicants want consideration of the references cited in the international search report, those references should be listed on PTO form 1449 and submitted for consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing because it can be interpreted in more than one way. Claim 1 may be interpreted as a sustained release pharmaceutical formulation of tramadol comprising tramadol or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable acidic substance or salt thereof.

Claim 1 may also be interpreted as a sustained release formulation of tramadol comprising a compound of tramadol or pharmaceutically acceptable salt of tramadol and a pharmaceutically acceptable acidic substance or salt thereof.

Claim 1 may also be interpreted as a sustained release formulation of tramadol comprising tramadol or its pharmaceutical salt associated with a pharmaceutically acceptable acidic substance or salt thereof.

Claim 1 is confusing because it is not clear what "formed in situ" does to the formulation.

Claim 1 is confusing because it is not clear what the "compound" is in the claim; and since it is not clear what the compound is, it is unclear if the solubility property is directed to tramadol or to the association of tramadol and the pharmaceutically acceptable acidic substance.

Clarification is respectfully requested.

For examination purposes, claim 1 is interpreted as a sustained release formulation comprising tramadol or it pharmaceutical salt and a pharmaceutically acceptable acidic substance or a salt thereof. Since the claim recites tramadol or its salt and a pharmaceutically acceptable acidic substance or its salt, the recited solubility would be an inherent property.

Claim 10 is vague and indefinite as it recites the "tramadol or the salt of tramadol is present in excess" but gives no units such as weight, moles or volume. For examination purposes, the "excess" in claim 10 is interpreted as weight excess.

Clarification is respectfully requested.

The recitation of "partially sustained-release" in claim 27 renders the claim indefinite because partially sustained release is not art recognized and one would recognize sustained release, controlled release, pulse release and rapidly disintegrating.

Clarification is respectfully requested.

Applicants may overcome this rejection by amending claim 27 where the term "partially" in line 1 is deleted.

For examination purposes claim 27 is interpreted as a method for preparing a sustained release oral formulation where the method comprises mixing tramadol or its pharmaceutically acceptable salt and acidic substance or its pharmaceutically acceptable salt.

Claims 12 and 18 recite the phrase "as a compound formed in situ" in line 3 and it is not clear how that phrase relates to equimolar amounts of tramadol and acidic substance in said claims.

Any remaining claims are rejected as depending on an indefinite claim.

Other Matters: In claim 10, it appears that after excess, "or" should be ---of---

Tramadol in line 2 of claim 11, lacks an ---l---

Moistening is spelled "mostening" in line 6 of claim 27

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-11, 13, 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Betzing et al. (US 5,776,492).

Betzing discloses formulations comprising tramadol HCl, microcrystalline cellulose, sodium saccharin, micro-dispersed (colloidal) silica, flavor agent and magnesium stearate (examples 1-4) and in example 5, the formulation further comprises cross-linked polyvinyl pyrrolidone. In all examples 1-5, tramadol HCL is 10.000 gram and sodium saccharin is 2.000 gram showing an excess tramadol HCl in weight over the sodium saccharin in weight. Instant claim 1 is directed to a sustained release formulation comprising tramadol or it pharmaceutical salt and a pharmaceutically acceptable acidic substance or a salt thereof and in claim 9, the salt of acidic substance is selected from the group consisting of salt of diclofenac, naproxen, acetylsalicylic acid, salicylic acid, benzoic acid, saccharin, cyclamate and acesulfame. In the prior art sodium saccharin is a salt of acidic substance according to the definition given in claim 9.

Instant claim 1 is a sustained release formulation and dependent claims 22 and 23 recite rapidly disintegrating tablets. Although the prior art is silent on the sustained release aspect of the formulation, there is no recitation in the instant claims that would exclude sustained release characteristics from the formulation of the prior art since the formulation of the prior art and the examined claims are the same. The sustained release aspect of the formulation would flow naturally from the use of the formulation. With respect to the solubility recited in claims 1 and 3-5, formulations comprising similar or same compositions would inherently have the same

solubilities. With regards to claim 11 and 13, formulations comprising same compositions would inherently have the same release profile because the release profile would flow naturally form the use of the formulation. Thus the teachings of Betzing meet the limitations of the claims.

7. Claims 1-8, 10-13, 19, 21, 22, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Raffa (US 5,516,803).

Raffa discloses a composition comprising tramadol and nonsteroidal anti-inflammatory drug (abstract). Raffa teaches that formulating opioids with non-opioid analgesic agents reduces side effects of opioids while producing equivalent degree of analgesia and while requiring less of the opioid (column 2, lines 1-6). Specifically, Raffa teaches formulation comprising tramadol and ibuprofen (example 1-3) and suggests that naproxen, tolmetin, diclofenac, etodolac or propionic acid derivatives, of which ibuprofen is the most preferred can also be combined with tramadol (column 3, line 60 to column 4 line 41). The weight ratio of tramadol to NSAID is from about 1:1 to 1:200, and synergistic effects results from said combination and the level or degree of said synergistic effects is dependent on the ratio of the tramadol to the NSAIDs (column 4, lines 41-58). Table 1 of Raffa shows a tramadol to ibuprofen weight ratio of 2:1 and example 1 and Table 1 also teaches tramadol to ibuprofen ratio of 1:1.

Raffa further discloses that solid oral preparations are formulated in the form of powders, capsules and tablets and comprise carriers such as starches, sugars, diluents, granulating agents, lubricants, binders and disintegrating agents (column 5, lines 35-38). Raffa discloses that the tablets may be sugar coated or enteric coated according to standard techniques. Regarding claim

19, the powder formulation of Raffa is particulate or microparticulate. Regarding claim 26, the method of controlling pain comprises administration of the pharmaceutical formulation of claim 1. Raffa teaches treating pain with a formulation of tramadol and ibuprofen (abstract and example 4). Since the method of the instant application is a mere administration of the formulation, and since controlling pain may be the same as treating pain, claim 26 is included in this rejection.

The instant claims are directed to compositions comprising tramadol or its pharmaceutically acceptable salt and pharmaceutically acceptable acidic substance or salt thereof. Although Raffa is silent on the sustained aspect of the formulation, there is no recitation in the examined claims that would exclude sustained release characteristics from the formulation of the prior art since the formulation of the prior art and the examined claims are the same and the release pattern would flow naturally from the use of the formulation. With respect to the solubility recited in claims 1 and 3-5, formulations comprising similar or same compositions would inherently have the same solubilities. Thus Raffa meets the limitations of the claims.

8. Claims 1-8, 10, 11, 13, 19, 20, 22, 24 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Oshlack et al. (US 5,958,452).

Oshlack discloses solid sustained release opioid analgesic preparation that comprises multiparticles (abstract). In one embodiment, when the sustained release composition has opioid analgesic as the therapeutic agent, additional therapeutic agent, which may or may not act synergistically with the opioid, is included and examples of the other therapeutic agents are non-steroidal anti-inflammatory agents of which ibuprofen, naproxen and diclofenac are examples

(column 8, lines 8-35). Examples 27 and 28 teach melt extrusion granulation and tablet compositions comprising tramadol HCl, tributyl citrate, stearyl alcohol, EUBRAGIT RSPO, talc and magnesium stearate. In examples 27 and 28 of Oshlack, the milligram weight of tramadol HCl is 200 and this weight is in excess of the 3.8 (example 27) and 3.4 (example 28) milligram weight of magnesium stearate. Magnesium stearate is a salt of the acidic substance of stearic acid and magnesium stearate meets the limitation of salt of pharmaceutically acceptable acidic substance recited in instant claim 1.

Oshlack discloses administering the composition to a patient in need thereof for pain relief (column 5, lines 1-9). Oshlack discloses that the preparation is melt extruded and shaped into beads, microspheres, seeds, pellets and in one embodiment the melt extruded multiparticles are encapsulated and in another embodiment, the extruded multiparticles are compressed into oral tablets using standard techniques " described in Remington's pharmaceutical sciences, (Arthur Oslo, editor), 1980, 1553-1593" (column 10, lines 49-63). In column 12, line 35 to column 13 line 54, Oshlack describes the melt-extrusion techniques and general pellet manufacturing procedure that is employed in making the sustained release preparations.

The weight of tramadol HCl is in excess of the weight of magnesium stearate as disclosed in examples 27 and 28. With respect to the solubility recited in claims 1 and 3-5, formulations comprising similar or same compositions would inherently have the same solubilities. Thus Oshlack meets the limitations of the claims.

9. Claims 1-8, 10, 19, 20, 22, 24 and 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Oshlack et al. (US 5,958,452).

The teaching of Oshlack is described above. The art is also applied under 35 U.S.C. 102(a) and same reasoning is applicable here. Oshlack anticipates the claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 9 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa (US 5,516,803).

Raffa teaches the composition of the invention except that Raffa does not specifically teach a composition comprising tramadol and acidic substance where the acidic substance is selected from diclofenac, naproxen, acetylsalicylic acid, salicylic acid, benzoic acid, saccharin, cyclamate and acesulfame as in claim 9. Regarding the limitation of microparticles in claim 20, Raffa discloses composition that is formulated into powder, which is particulate, and the difference between particles and microparticles is in the size. But differences in size do not distinguish microparticles from the particles of the powder formulation unless the size of the particles is critical to the pharmaceutical composition. It is noted that there is no recitation of the specific size(s) of the particles. Regarding claim 9, Raffa does not specifically teach a composition comprising tramadol and acidic substance where the acidic substance is selected from diclofenac, naproxen, acetylsalicylic acid, salicylic acid, benzoic acid, saccharin, cyclamate and acesulfame. In this claim the acidic substance is selected from a list of acidic substances.

Although the list of therapeutic agents suggested by Raffa is longer than the list of acidic substances recited in claim 9, Raffa nonetheless suggests combining naproxen sodium, and ibuprofen, zomepirac sodium, piroxicam, diflunisal, proquazone, diclofenac, etodolac or nabumetone NSAIDs (column 4, lines 13-37) with tramadol and specifically exemplifies the formulation with ibuprofen. Since Raffa specifically teaches tramadol/NSAID formulations, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare other tramadol/NSAID formulations according to the teaching of Raffa. One having ordinary skill in the art would have been motivated to combine tramadol with the other NSAIDs suggested by Raffa because substituting the other NSAIDs of naproxen sodium, zomepirac sodium, piroxicam, diflunisal, proquazone, diclofenac, etodolac or nabumetone for ibuprofen is expected to produce a tramadol formulation that requires less amount of tramadol for the production of equivalent degree of analgesia.

12. Claims 27-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa (US 5,516,803) in view of known method of making tablets described in eighteenth edition of Remington's Pharmaceutical Sciences, 1990, pages 1641-1647.

The teachings of Raffa are discussed under 35 U.S.C. 102 where it was discussed that powder, capsule and tablet solid preparations comprise carriers such as starches, sugars, diluents, granulating agents, lubricants, binders and disintegrating agents. However, Raffa does not exemplify preparation of tramadol/ibuprofen tablets. But methods of making tablets are known as disclosed and taught in the eighteenth edition of Remington's Pharmaceutical Sciences. Remington specifically teaches wet-granulation method, fluid-bed granulation method, dry-granulation method, direct compression and related granulation processes (pages 1641-1647).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the preparation of Raffa into tablets employing granulation methods disclosed in the eighteenth edition of Remington's Pharmaceutical Sciences, 1990, pages 1641-1647, since utilizing the disclosed methods in Remington is expected to produce tablets.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1, 2 and 6-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-7 and 11 of co-pending Application No. 10/016,130. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 1 is directed to a pharmaceutical composition comprising tramadol or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable acidic substance or salt thereof that is defined in instant claim 2 as a pharmaceutically active substance, which is further defined as diclofenac sodium in instant claim 14. Co-pending claim 1 teaches a formulation comprising an active substance tramadol or pharmaceutically acceptable salt thereof, and a second active substance diclofenac or

pharmaceutically acceptable salt thereof and the two active substances are in separate subunits. But co-pending claim 11 allows for mixing of the active substances as the active substances are in a controlled release formulation. Furthermore, tramadol and diclofenac would be released from formulations comprising tramadol or its salt and diclofenac or its sodium salt during use (see examined claims 11,13 and 17). Tramadol HCl and diclofenac sodium are soluble in water (see twelfth edition of the Merck Index, 3132 for diclofenac sodium and 9701 for tramadol HCl). Also, claims 5-7 of the co-pending application teach the ratio of tramadol to diclofenac as from 1:4 to 4:1 while the instant claims 15 and 16 recite a ratio of from 0.5:1 to4:1, and equimolar amounts of the tramadol and diclofenac sodium represents a molar ratio of 1:1 that is the beginning ratio in co-pending claim 7. The difference between the co-pending claims and the examined claims is that the ratio of tramadol to diclofenac in the co-pending application is encompassed in the ratio of tramadol to diclofenac in the instant claims. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the formulation in the co-pending claims since the range in the ratio of tramadol to diclofenac in co-pending application is allowed in the range of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 17 and 38 are dependent claims. The prior art does not teach composition comprising tramadol hydrochloride and diclofenac sodium. These claims are also rejected under 35 U.S.C. 112, second paragraph. Claims 17 and 38 would be allowable if the rejection under 35 U.S.C. 112, second paragraph is overcome and if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

16. The following prior art made of record is considered pertinent to applicant's disclosure and the relevance to the claimed invention is discussed below.

Mauskop (US 5,914,129) discloses magnesium containing analgesic oral composition for the treatment/alleviation of pain, and specifically migraine headache pain (abstract). Solid formulations of the composition are capsules, catchets or tablets and powder or granules; liquid formulations are solution or suspension in aqueous liquid or non-aqueous liquid and oil-in-water or water-in-oil emulsions; and solid formulation of tablet and capsules are preferred with tablet being the most preferred (column 6, lines 12-21). In a particular embodiment of Mauskop, the magnesium containing analgesic composition includes at least two different non-opioid analgesic agents, at least two different opioid analgesic agents or at least one non-opioid analgesic agent and at least one opioid analgesic agent and it is believed that a combination of non-opioid analgesic agents or opioid analgesic agents or a combination of non-opioid and opioid analgesic agents act synergistically to relieve pain (column 3, lines 47-54). In the case where the pharmaceutical composition comprises a combination of a non-opioid analgesic agent and an opioid analgesic agent (claim 6); the non-opioid analgesic agent of ibuprofen, naproxen and diclophenac (diclofenac sodium) are included in the list of non-opioid analgesic agents provided (claims 1-4, 6 and 15) and the opioid analgesic agents of tramadol is included in the list of opioid analgesic agents provided (claims 1, 4, 5, 6 and 17). Mauskop, in column 6, lines 18-31, discloses how the tablet is formulated. While Mauskop suggests the combination of opioid analgesic and non-opioid analgesic to synergistically act to relieve pain and while tramadol in included in the list provided, there is no specific teaching where tramadol is the principal opioid analgesic that is combined with any of the non-opioid analgesics.

17. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is respectfully requested in correcting any errors of which applicant may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is 703-308-8374. The examiner can normally be reached on 7 a.m. to 3:30 p.m. (Monday to Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Blessing Fubara MB Fubara
Patent Examiner
Tech. Center 1600
January 10, 2003